PATENT
CUSTOMER NO. 32425

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:
John B. Harley *et al.*

Serial No.: 09/500,904

Filed: February 9, 2000

For: DIAGNOSTICS AND THERAPY OF EPSTEIN-BARR VIRUS IN AUTOIMMUNE DISORDERS

Group Art Unit: 1648

Examiner: S. FOLEY

Atty. Dkt. No.: OMRF:051US

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37 C.F.R. § 1.8

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Steven L. Highlander

SUBSTITUTE BRIEF ON APPEAL

Commissioner for Patents
P.O. Box 1450
Alexandria, Virginia 22313-1450

Sir:

This substitute brief on appeal is filed in response to Notice of Non-Compliance and Advisory Action mailed on June 15, 2004, to which a response is due on October 15, 2004, by virtue of the enclosed petition for extension of time and payment of fees. If the fees are missing or deficient, appellants authorize the Commissioner to debit Fulbright & Jaworski L.L.P. Deposit Account No. 55-1212/OMRF:051US/SLH.

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I. Real Party in Interest

The real party in interest of this application are the assignees, the Oklahoma Medical Research Foundation, Oklahoma City, OK, the Board of Regents of the University of Oklahoma Health Science Center, Oklahoma City, OK, and the licensee, JK Autoimmunity, Inc., Oklahoma City, OK.

II. Related Appeals and Interferences

The following related appeals are known to appellant, the undersigned, or appellants' assignee or licensee, which directly affect, which would be directly affected by, or which may have a bearing on the Board's decision in this appeal:

U.S. Serial No. 08/475,955 – a copy of the decision in this application was placed in the present file.

U.S. Serial No. 08/781,296 – an appeal was mooted in favor of reopened prosecution.

III. Status of Claims

Claims 6-10 and 19-22 are pending and on appeal. The claims are listed in Appendix A to this brief.

IV. Status of Amendments

An amendment after final was submitted on April 5, 2004, with the original Brief on Appeal. That amendment was entered though it was believed not to impact the remaining rejection under 35 U.S.C. §112, first paragraph.

V. Summary of Invention

Differences have been identified in the immune responses to Epstein-Barr infection between individuals who develop of specific autoimmune disease and those who do not. Specification at page 8, lines 20-22. These differences are used in the claimed diagnostic assay kits and methods of use thereof to distinguish those who are at greater risk of developing specific autoimmune diseases from those who are a lesser risk. Specification at page 8, lines 22-24. Individuals who are not at as great a risk for developing autoimmune disease can be identified by reactivity to various peptides, for example, as demonstrated in the examples where individuals who are not prone to develop lupus are characterized by antibodies to SEQ ID NO:7. Specification at page 2, lines 15-19. Subsets of antigenic peptides can be used to identify patients at risk for particular clinical manifestations or patients in particular prognostic groups. Specification at page 26, lines 21-23. The peptides can be used in combination assays, such as the solid phase assay, to classify patients. Specification at page 26, lines 23-24.

VI. Issues

Whether the claims are properly rejected under 35 U.S.C. §112, first paragraph for alleged lack of enablement?

Whether the claims are properly rejected under the judicially created doctrine of obviousness-type double-patenting over claim 35 of U.S. Serial No. 08/781,296.

VII. Grouping of Claims

The claims do not stand or fall together, as discussed below.

VIII. Argument

A. Standard of Review

As an initial matter, appellant notes that findings of fact and conclusions of law by the U.S. Patent and Trademark Office must be made in accordance with the Administrative Procedure Act, 5 U.S.C. § 706(A), (E), 1994, and *Dickinson v. Zurko*, 527 U.S. 150, 158 (1999). Moreover, the Federal Circuit has held that findings of fact by the Board of Patent Appeals and Interferences must be supported by "substantial evidence" within the record. *In re Gartside*, 203 F.3d 1305, 1315 (Fed. Cir. 2000). In *In re Gartside*, the Federal Circuit stated that "the 'substantial evidence' standard asks whether a reasonable fact finder could have arrived at the agency's decision." *Id.* at 1312. Accordingly, it necessarily follows that an Examiner's position on Appeal must be supported by "substantial evidence" within the record in order to be upheld by the Board of Patent Appeals and Interferences.

B. Rejection Under 35 U.S.C. §112, First Paragraph

Claims 6-10 and 19-22 stand rejected under the first paragraph of §112 as lacking an enabling disclosure. According to the examiner, while the specification is enabling for detecting EBV, it does not enable predicting the risk of developing lupus by detecting the presence of EBV. Once again, appellants traverse.

An invention must have utility. This requirement can be found in 35 U.S.C. § 101 which states, "Whoever invents or discovers any new and *useful* process or...composition of matter...may obtain a patent..." (emphasis added). This requirement is also implicitly found in 35 U.S.C. § 112 which requires the specification to provide a written description for "making and *using*" the claimed subject matter.

Whether the utility requirement comes from 35 U.S.C. § 101 or 35 U.S.C § 112, the standard to be applied is the same. *Ex parte Maas*, 14 USPQ2d 1762, 9 USPQ2d 1746, 1747

(Bd. Pat. App. & Int'f 1987). The *Maas* court stated, "the issue under 35 U.S.C § 112 relating to an enabling disclosure is subsumed within the issue under 35 U.S.C § 101 relating to patentable utility." Any analysis of claim under 35 U.S.C § 112, first paragraph relating to the use of the claimed subject matter, need only meet the standards of the utility requirement of 35 U.S.C § 101 because if the claimed subject matter meets the utility requirement it is presumed to meet the enablement requirement of use.

To meet the utility requirement the invention must simply have a "practical utility" in the "real world sense." (*Nelson v. Bowler*, 626 F.2d 853 (CCPA, 1980)). Any use which gives immediate benefit to the public is sufficient to be a "practical utility". *Id.* at 856. It is clear that for an invention to have "practical utility" it must be operative. However, to fail the utility requirement the claimed subject matter must be "totally incapable of achieving a useful result. ("In short, the defense of non-utility cannot be sustained without proof of total incapacity.") (*Brooktree Corp v. Advanced Micro Devices, Inc.*, 977 F.2d 1555 (Fed. Cir. 1992). See also *E.I. duPont De Nemours and Co. v. Berkley and Co.*, 620 F.2d 1247, 1260 n.17, 205 USPQ 1, 10 n.17 (8th Cir. 1980). An assertion of utility is sufficient to meet the utility requirement unless the assertion is "incredible in the light of the art or factually misleading." (*In re Citron,* 325 F.2d 1389 (CCPA, 1963)).

The Court of Appeals for the Federal Circuit (CAFC) has described the legal standard for enablement under § 112, first paragraph, as whether one skilled in the art could make and use the claimed invention from the disclosures in the patent coupled with information known in the art without undue experimentation (See, *e.g.*, *Genentech, Inc. v. Novo Nordisk A/S*, 108 F3d at 165, 42 USPQ2d at 1004 (quoting *In re Wright*, 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); see also *In re Fisher*, 427 F.2d at 839, 166 USPQ at 24; *United States v. Telectronics*,

Inc., 857 F.2d 778 (Fed. Cir. 1988); *In re Stephens*, 529 F.2d 1343 (CCPA 1976)). The fact that experimentation may be complex does not necessarily make it undue, if the art typically engages in such experimentation (*M.I.T. v. A.B. Fortia*, 774 F.2d 1104 (Fed. Cir. 1985)). In addition, as affirmed by the Court in *Spectra-Physics, Inc. v. Coherent, Inc.*, 827 F.2d 1524 (Fed. Cir. 1987), a patent need not teach, and preferably omits, what is well known in the art.

Whether making or using the invention would have required undue experimentation, and thus whether the disclosure is enabling, is a legal conclusion based upon several underlying factual inquiries. See *In re Wands*, 858 F.2d 731, 735, 736-737, 8 USPQ2d 1400, 1402, 1040 (Fed. Cir. 1988). As set forth in *Wands*, the factors to be considered in determining whether a claimed invention is enabled throughout its scope without undue experimentation include the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in the art, the predictability or unpredictability of the art, and the breadth of the claims. In cases that involve unpredictable factors, "the scope of the enablement obviously varies inversely with the degree of unpredictability of the factors involved." *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation 'must not be unduly extensive.' *Atlas Powder Co. v. E.I. DuPont De Nemours & Co.*, 750 F.2d 1569, 1576, 224 USPQ 409, 413 (Fed. Cir. 1984).

> The test is not merely quantitative, since a considerable amount of experiment is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which

the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed.

Ex parte Jackson, 217 USPQ 804, 807 (1982)

As stated in the MANUAL OF PATENT EXAMINING PROCEDURE §2164.04 (7th ed. 1998), *citing In re Wright*, 999 F.2d 1557, 1562 (Fed. Cir. 1993), the examiner has the initial burden to establish a reasonable basis to question the enablement of the application.

> A specification disclosure which contains a teaching of the manner and process of making and using an invention in terms which correspond in scope to those used in describing and defining the subject matter sought to be patented **must be taken as being in compliance with the enablement requirement** of 35 U.S.C § 112, first paragraph, unless there is a reason to doubt the objective truth of the statements contained therein which must be relied on fro enabling support.

Id. at § 2164.05 (emphasis added).

The examiner has set forth an analysis of the relevant enablement issues including the seven factors set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988). However, in assessing the *Wands* factors set forth at pages 4-6 of the final Office Action, it is notable that the only factors the examiner can point to that allegedly mitigate against enablement relate to the state of the art, and the entire argument is premised on the observation "the prior art does not recognize a nexus between the presence of EBV and developing lupus." This comment is quite perplexing since the absence of a teaching in the prior art of the claimed invention is ***always*** a prerequisite for patentability. Thus, the lack of such teachings actually supports the patentability of the present invention, and says nothing about enablement.

Next, the examiner argues that there would be no way to select proper controls as "a majority that have been exposed to EBV ... do not have lupus." This misses the point of the invention entirely, since appellants are not merely correlating the presence of EBV with lupus. Rather, the invention relies on the presence of antibody reactivity to ***certain epitopes that are correlated with the development of autoimmunity***. This is an entirely different phenomenon than simply detecting EBV. Thus, the presence of antibodies to ***other*** epitopes in EBV-challenged, but otherwise ***healthy*** patients, would not, in any way, confound the diagnosis.

The examiner also makes a totally unwarranted conclusion, based on Marchini *et al.*, that the specification is deficient in not relying on anti-EBNA antibodies to diagnose lupus. Once again, the fact that the prior art does not presage the invention is merely further reason to find the claims both novel and nonobvious. It does not, without more, say ***anything*** about the enablement of the present invention. Similarly, Carson's teaching that there are many obstacles to predicting autoimmune disease does not bear upon whether appellants' methods are enabled.

The remaining *Wands* factors are nothing more than a restatement of the examiner's initial premise, set forth above, that the prior art does not corroborate appellants' invention. However, that is not the standard for enablement. In essence, the entire rejection boils down to the single statement that "[a]lthough data in the specification demonstrates cross-reactivity with specific peptides between EBV and lupus, the assumption that EBV causes or that it is indicative of a possible development of lupus is unsubstantiated." In other words, the examiner simply disbelieves the underlying principle of the invention, and without any evidence ***regarding the claimed invention per se***, rejects all of the claims. As such, it is manifestly clear that the examiner has failed to carry the burden in establishing that appellants' presumptively enabling

disclosure is defective. *In re Marzocchi*, 169 USPQ 370 (CCPA 1971). Reversal of the rejection of this ground alone is respectfully requested.

C. Submission Under 37 C.F.R. §1.195

In addition to the information provided in the instant specification, appellants also are now submitting a manuscript (accompanied by a supporting declaration under 37 C.F.R. §1.132), completed only after submission of the previous appeal brief, and entitled "An altered immune response to Epstein-Barr virus suggests a link to systemic lupus erythematosus," by McClain *et al.* This paper is supported by the declaration of the inventors, who are all authors on the paper. As discuss therein, 36 SLE patients and their matched EBV positive controls were demonstrated to produce anti-EBV-VCA antibodies. All 36 SLE patients produced antibodies against a 70 kD band in the EBV infected lysates (from B95-8 or Jijoye). Of the 36 sera from EBV-positive controls (matched on age, sex, and race), 11 (31%) did not produce detectable antibodies which recognized EBNA-1 from either the B95-8 or the Jijoye cell lines. Anti-EBNA-1 antibodies are therefore associated with SLE (OR=30.4, χ^2=13.3, $p<0.005$, CI 95% 1.7 to 544).

To explore differences in the humoral responses between cases and controls, expressed fragments containing the N-terminal (amino acids 1-89), middle (amino acids 90-330), and carboxyl terminal (amino acids 331-641) regions of EBNA-1 were tested. Twenty pediatric SLE patient sera and 20 sera from their matched, EBV-positive controls were randomly selected. Compared to the control sera, the SLE patients had relatively greater average binding to the N-terminal fragment (containing the glycine-arginine rich segment) (mean OD=0.451 versus 0.268) and to the carboxy terminal fragment (OD=0.844 versus 0.296). Controls (OD=0.779) have higher average binding to the glycine-alanine rich middle segment (containing the multiple glycine-alanine repeats) when compared to the SLE patients (OD=0.396). All pairwise case-control comparisons are significant by student's T test ($p<0.001$).

The 20 lupus patient sera tested bound many different overlapping octapeptides of the EBNA-1 protein, while normal EBV-negative individuals do not. Binding of a representative SLE patient serum shows the many epitopes typically bound in the amino and carboxyl terminal regions of EBNA-1 in most of these pediatric SLE sera. In contrast, the anti-EBV-VCA positive normal control serum illustrates the stark differences usually observed between cases and controls, which is also demonstrated by the mean binding of SLE and their control sera. Anti-EBV-VCA negative control sera showed no significant reactivity (average background binding OD=0.118).

Among epitopes selectively bound by the SLE pediatric sera, amino acids 40-53 (GRGRGRGRGRGGR), known as the (GR_X) region, and amino acids 398-404 (PPPGRRP) are commonly targeted, although this latter epitope just fails to achieve statistical significance when all SLE patients are averaged (binding is 1.98 standard deviations above the normal mean). However, all of these anti-PPPGRRP positive sera also bind Sm in the standard solid phase assay (data not shown). Some variation in the binding of individual SLE patient sera to these octapeptides does occur. For instance, about 67% of the SLE patient samples bind PPPGRRP. Tested pediatric SLE samples, however, do not significantly bind (>2 S.D.), the regions comprising the (GA_X) repeats that are the primary target of the normal humoral immune response.

In contrast the normal, EBV-positive pediatric controls reveal an entirely different binding pattern to the overlapping octapeptides of EBNA-1. Normal children and teenagers make antibodies primarily against two epitopes of the EBNA-1 protein (both of which are present in the middle recombinant EBNA-1 fragment). These epitopes consist of amino acids 101-113 (GGAGAGGGAGAGG) and amino acids 140-155 (GGAGAGGGAGAGGGAG),

neither of which are recognized by the pediatric SLE patient sera. Furthermore, a group of five EBV-positive polymyositis patients show a nearly identical, limited response to the octapeptides of EBNA-1 as that seen in normal EBV-positive controls (data not shown). Unlike the SLE pediatric sera tested, non-SLE but EBV-positive individuals have a nearly uniform, almost monotonously replicated binding pattern, as is demonstrated by the close similarity between the representative example and mean binding. In fact, the mean binding pattern generally observed in the pediatric controls is different and virtually mutually exclusive from the pattern generated by the SLE pediatric patient sera. This result strongly suggests that the molecular and cellular immunoregulatory events that lead to anti-EBNA-1 antibodies are significantly different in the pediatric SLE patients than they are in their normal pediatric matched controls.

CMV-IE was chosen as a control antigen since it is a DNA binding protein found in another life-long, common herpes virus infection and since CMV-IE is known to induce an antibody response in normal CMV-infected individuals. Both SLE patients and normal individuals recognize multiple, almost identical epitopes of CMV-IE. In contrast to the distinct qualitative differences between SLE and normal immune responses to EBNA-1, the SLE sera bind the same epitopes of the CMV-IE octapeptides less avidly than control sera.

The authors, based on these data, conclude as follows that:

> We have tested whether the demonstrated association between SLE and EBV originates with the anti-EBV humoral immune responses. Since previous data suggest a molecular mimicry mechanism between EBNA-1 and Sm B' (11,22-25,34), EBNA-1 was the obvious focus for our experimental approach. Now, we further substantiate these ideas by demonstrating that pediatric SLE patients and matched normal individuals make distinct antibody responses against EBNA-1 and that anti-EBNA-1 is associated with SLE. In addition, these EBNA-1 data are in agreement with the previously reported three epitopes of EBNA-1 reactive in SLE but not in normals (23), done with a less discriminating technical approach. That EBNA-1 has a very unusual antigen presentation (12-15) offers many avenues to explore the pathophysiology and systemic autoimmunity of SLE. Certainly, potential mechanisms for induction of autoimmunity by EBV have been

demonstrated, and the differences in normal and lupus immune responses outlined here are consistent with the possibility that those mechanisms play a role in the initiation or perpetuation of SLE.

Discussion, last paragraph. Thus, it is submitted that this additional evidence, which has only recently been obtained, further supports appellants' position regarding enablement, and provides another reason that the rejection should be reversed.

D. Rejection for Obviousness-Type Double-Patenting

Claims 6-10 and 19-22 are provisionally rejected over claim 35 of copending application U.S. Serial No. 08/781,296. As indicated previously, appellants are prepared to provide a terminal disclaimer or cancel the competing claim from the '296 application at such time as this rejection becomes non-provisional.

IX. Conclusion

In light of the foregoing, appellants respectfully submit that all claims are enabled and therefore, reversal of the rejection is respectfully requested.

Respectfully submitted,

October 15, 2004
Date

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APPENDIX A – COPY OF PENDING CLAIMS

Claims 1-5 (cancelled)

6. A diagnostic test to predict the risk of developing lupus comprising

reagents which can be used to detect levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in a patient, wherein the reagents used to detect antibodies to peptides from Epstein-Barr virus are peptides of up to forty amino acids in length comprising an amino acid sequence selected from the group consisting of PPPGRRP (SEQ ID NO:1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR (SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO: 107), NPKFENIA (SEQ ID NO: 108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSFDDG (SEQ ID NO:49), PPWFPPMVEG (SEQ ID NO:50) or the peptide consisting of GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), or antibodies reactive with these peptides, and

control samples from individuals not at risk of developing lupus, and

means for determining the differences in levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in of a patient and control samples to distinguish individuals at higher risk of developing lupus from those at lower risk of developing lupus.

7. The diagnostic test of claim 6 wherein the reagents are used in assays selected from the group of assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, and assays based on cell surface antigen.

8. The diagnostic test of claim 6 wherein the reagents used to detect antibodies to peptides from Epstein-Barr virus are selected from the group consisting of PPPGRRP (SEQ ID NO: 1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR (SEQ ID NO: 103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGA1 (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSFDDG (SEQ ID NO:49), and PPWFPPMVEG (SEQ ID NO:50).

9. The diagnostic test of claim 8 comprising reagents for detection of antibodies to GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).

10. The diagnostic test of claim 6 for testing patients identified with or at risk of developing systemic lupus erythematosus comprising control samples from individuals with systemic lupus erythematosus.

Claims 11-18 (cancelled)

19. A method for determining the likelihood that an individual has lupus induced by Epstein-Barr virus, or is at risk for developing lupus, comprising

obtaining a sample from the individual to be tested,

mixing the sample with reagents which can be used to detect levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in a patient,

analyzing the sample, and

comparing the analysis of the sample with results obtained with control samples from individuals not at risk of developing lupus to determine if the differences in levels of antibodies to Epstein-Barr virus, indicators of Epstein-Barr infection of cells, or levels of Epstein-Barr DNA or protein in the individual and control samples indicates the individual is at a higher risk of developing lupus than controls who are at lower risk of developing lupus.

20. The method of claim 19 wherein the reagents are used in assays selected from the group of assays based upon the relative presence of an antibody, assays based on cellular proliferation, assays based on molecular binding, assays based on cytokine production, assays based on skin reaction, and assays based on cell surface antigen.

21. The method of claim 19 wherein the reagents used to detect antibodies to peptides from Epstein-Barr virus are selected from the group consisting of PPPGRRP (SEQ ID NO: 1), GRGRGRGG (SEQ ID NO:2), RGRGREK (SEQ ID NO:3), GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7), GPQRRGGDNHGRGRGRGRGGGRPG (SEQ ID NO:98), GGSGSGPRHRDGVRRPQKRP (SEQ ID NO:25), RPQKRPSC (SEQ ID NO:26), QKRPSCIGCKGTHGGTG (SEQ ID NO:27), GTGAGAGARGRGG (SEQ ID NO:99), SGGRGRGG (SEQ ID NO:100), RGGSGGRRGRGR (SEQ ID NO:101), RARGRGRGRGEKRPRS (SEQ ID NO:102), SSSSGSPPRRPPPGR (SEQ ID NO:103), RPPPGRRPFFHPVGEADYFEYHQEG (SEQ ID NO:104), PDVPPGAI (SEQ ID NO:33), PGAIEQGPA (SEQ ID NO:34), GPSTGPRG (SEQ ID NO:105), GQGDGGRRK (SEQ ID NO:37), DGGRRKKGGWFGKHR (SEQ ID NO:38), GKHRGQGGSN (SEQ ID NO:106), GQGGSNPK (SEQ ID NO:107), NPKFENIA (SEQ ID NO:108), RSHVERTT (SEQ ID

NO:109), VFVYGGSKT (SEQ ID NO:110), GSKTSLYNL (SEQ ID NO:111), GMAPGPGP (SEQ ID NO:46), PQPGPLRE (SEQ ID NO:47), CNIRVTVC (SEQ ID NO:48), RVTVCSFDDG (SEQ ID NO:49), and PPWFPPMVEG (SEQ ID NO:50).

22. The method of claim 19 wherein the individual is tested for the presence of antibodies to GAGAGAGAGAGAGAGAGAGAGA (SEQ ID NO:7).